PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Benefits and harms of lower blood pressure treatment targets – systematic review and meta-analysis of randomized placebo-controlled trials
AUTHORS	Brunström, Mattias; Carlberg, Bo

VERSION 1 – REVIEW

REVIEWER	Wuxiang Xie Peking University Clinical Research Institute
REVIEW RETURNED	09-Oct-2018

GENERAL COMMENTS	Thank you for the opportunity to review this interesting manuscript by Drs Brunström and Carlberg. I applaud the authors for all the hard-work and thought process put into it. Generally speaking, the manuscript is clearly presented and add some new knowledge to existing literature. I have several minor concerns: 1. As the authors have acknowledged in the limitations, some of the participants with an SBP >140 or <130. This is one of the most important limitations and I assume the authors cannot obtain the percentage of these participants. 2. Why randomized double-blind trials were limited to those with >= 1000 patient-years of follow-up. To avoid the problem of small sample bias? 3. In both primary and secondary preventive meta-analyses, the baseline SBP in trials was closed to 140 mmHg (138 and 137), but the mean values of SBP at the end of treatment were not reported. I assume the authors also cannot give the percentage of participants with an SBP<130 mmHg (achieved target) in groups of intervention and placebo. 4. In my view, the conclusion in the abstract is reasonable. However, the evidence from this meta-analysis is not strong enough to question the recent shift in SBP treatment target (the first paragraph in Discussion).

REVIEWER	Changwei Li Department of Epidemiology & Biostatistics, University of Georgia College of Public Health, USA
REVIEW RETURNED	30-Oct-2018

GENERAL COMMENTS	Very well conducted study on an important topic. I only have several points need to be addressed: 1. I think the authors should include “coronary” in addition to “myocardial”, and why not including heart failure in the search terms? 2. Is treatment effect associated with proportion of 1) women, 2) DM, 3) baseline BP, or 4) age? 3. Is treatment effect differ by classes of antihypertensive medications?

REVIEWER	Rochelle Fu Oregon Health & Science University USA
REVIEW RETURNED	04-Feb-2019

GENERAL COMMENTS	Introduction The rational of this review is not clear. The authors conducted a systematic review including only randomized double-blinded placebo-controlled trials, aiming to reduce the risk of bias in the previous review where only non-blinded trials were included. However, these two types of trials were different in their objectives. The reason that the randomized double-blinded placebo-controlled trials did not show a treatment effect, may be due to the fact that there is only a minor decrease in SBP, instead of performance bias. If a lower SBP was achieved in the blinded trials (say, < 120 mm Hg, as in the SPRINT Trial), the results may be different. The manuscript does not provide adequate justification to conduct this systematic review. Methods Stratifying the results by primary vs. secondary prevention is a strength of this review. Page 8, 2nd paragraph -- ITT principle: so the included studies reported results based on ITT principle? Otherwise, it is hard to use this principle based on study level data. A lot of sensitivity analyses were conducted on a small number of studies. Not sure they provided useful insights. Funnel plots and test for small study effects: the review had very specific inclusion/exclusion criteria and only included a highly selective group for studies. Also the number of studies is small and it is not clear what exactly the results mean. Discussion Page 13, first paragraph of discussion , last sentence, “Overall, the results presented here question the recent shift in SBP treatment goals from 140 mm Hg to 130 mm Hg for the majority of patients, seen on both sides of the Atlantic.” – Well, on average, the included studies did not achieve the 130 mm Hg target? Is it possible that the included studies did not see much efficacy due to the small decrease in SBP? Whether or not there is an issue in the new targeted SBP, it is not adequately addressed by the results of this review. The argument on potential performance bias (page 15) does not seem to be convincing either.

	The discussion on standardization was not very clear. The issues discussed should not happen with proper standardization. Many places in the text need more clarification. Here are a few examples: Page 7, first paragraph, "… because several antihypertensive agents are thought to have blood pressure independent effects on clinical outcomes in these settings". What are "blood pressure independent effects"? It helps to be more specific. Page 7, second paragraph, what does it mean "we used one of our recent, more comprehensive systematic reviews for study selection"? More accurate description is helpful. Similarly, Page 8, the last sentence of the first paragraph, please improve the clarity. ….. Page 17, "Although arguments can be made for including target-trials, lumping different populations and using standardization, all these approaches build on assumptions that the current analysis does not."

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1

1. As the authors have acknowledged in the limitations, some of the participants with an SBP >140 or <130. This is one of the most important limitations and I assume the authors cannot obtain the percentage of these participants.

Unfortunately, such an analysis would require individual patient data, not available to us.

2. Why randomized double-blind trials were limited to those with >= 1000 patient-years of follow-up. To avoid the problem of small sample bias?

Yes, this has been added to the methods section.

3. In both primary and secondary preventive meta-analyses, the baseline SBP in trials was closed to 140 mmHg (138 and 137), but the mean values of SBP at the end of treatment were not reported. I assume the authors also cannot give the percentage of participants with an SBP<130 mmHg (achieved target) in groups of intervention and placebo.

This is an important point. Unfortunately, we do not have access to proportions of participants above and below certain values. We acknowledge, however, that follow-up BPs are important for the interpretation of our results, and have therefore calculated weighted mean follow-up values for both treatment and control groups, reported in the first paragraph in the results section.

4. In my view, the conclusion in the abstract is reasonable. However, the evidence from this meta-analysis is not strong enough to question the recent shift in SBP treatment target (the first paragraph in Discussion).

We have rephrased that section and changed "question" to "do not support".

Reviewer: 2

1. I think the authors should include “coronary” in addition to “myocardial”, and why not including heart failure in the search terms?

The literature search in a systematic review is always about balancing sensitivity versus specificity. A very broad search will increase workload, and may offer little extra in terms of relevant trials. In this particular case, we included the search term “myocardial” to find myocardial infarctions, whereas coronary would have found lots of additional outcomes beyond the scope of this review.

To our knowledge, no randomized controlled trial in hypertension has used heart failure as the primary efficacy outcome; heart failure is usually a secondary outcome in trials assessing the effect on mortality, stroke, or myocardial infarction. Thus, we are confident that adding the term “heart failure” would not increase sensitivity, but would decrease specificity in an unfavorable way.

The literature search has not been revised.

2. Is treatment effect associated with proportion of 1) women, 2) DM, 3) baseline BP, or 4) age?

Associations with DM was assessed in metaregression analyses and found to be non-significant. Association with baseline BP within this tight BP range was not judged to be meaningful, for this we refer to our previous work (Brunström & Carlberg. JAMA Intern Med 2018). Exploring age and sex in any meaningful way would require individual patient data, to which we do not have access. We have added a statement addressing this in the limitations section.

3. Is treatment effect differ by classes of antihypertensive medications?

The drugs used in each of the included trials are presented in table 1. As evident from the table, all but two trials assessed the effect of RAAS inhibitors. We have added a comment about that in the limitations section; however further exploration in subgroup analyses would not be meaningful.

Reviewer: 3

Introduction
The rational of this review is not clear. The authors conducted a systematic review including only randomized double-blinded placebo-controlled trials, aiming to reduce the risk of bias in the previous review where only non-blinded trials were included. However, these two types of trials were different in their objectives. The reason that the randomized double-blinded placebo-controlled trials did not show a treatment effect, may be due to the fact that there is only a minor decrease in SBP, instead of performance bias. If a lower SBP was achieved in the blinded trials (say, < 120 mm Hg, as in the SPRINT Trial), the results may be different. The manuscript does not provide adequate justification to conduct this systematic review.

We partly agree with this comment. Blood pressure was lowered less (3.2 mm Hg for primary prevention; 4.2 mm Hg for secondary prevention) in the trials included in this review compared to the trials included in the ACC/AHA meta-analysis, restricted to target-trials (appr. 10 mm Hg for MACE in intensive target analysis). Thus, a less pronounced effect (about one third – 5 % relative risk reduction for MACE) would have been expected. However, the confidence intervals presented in our paper exclude such a risk reduction (95 % CI 0,96 to 1.06 for MACE). Thus, the difference in results between reviews cannot be explained solely by difference in magnitude of blood pressure lowering.

The minor decrease in BP is a limitation (addressed in discussion), but not an argument to abstain from performing this analysis.

The rational for performing this review was to validate the findings from the ACC/AHA analysis in a completely different study population, using a (in theory) more robust design. We have revised the introduction to more clearly specify the validation aspect.

Methods
Stratifying the results by primary vs. secondary prevention is a strength of this review.

We thank reviewer 3 for this acknowledgement.

Page 8, 2nd paragraph -- ITT principle: so the included studies reported results based on ITT principle? Otherwise, it is hard to use this principle based on study level data.

Yes. Or else, number of events and number of randomized participants with follow-up data were extracted separately, after which (modified) ITT analyses were calculated by hand.

A lot of sensitivity analyses were conducted on a small number of studies. Not sure they provided useful insights.

We agree that no major conclusions should be drawn from these analyses. We do, however, think it is better to report them than to exclude them from the manuscript, to be as transparent as possible. We have added a sentence in the main text, emphasizing that these should be interpreted cautiously.

Funnel plots and test for small study effects: the review had very specific inclusion/exclusion criteria and only included a highly selective group for studies. Also the number of studies is small and it is not clear what exactly the results mean.

Agree. Forest plots should always be interpreted carefully, and more so when few trials are available. Neither plots or tests can exclude small-study bias, and this has been emphasized in the revised text. As with the previous comment, however, we do not see that the manuscript would improve if these plots were removed.

Discussion
Page 13, first paragraph of discussion , last sentence, “Overall, the results presented here question the recent shift in SBP treatment goals from 140 mm Hg to 130 mm Hg for the majority of patients, seen on both sides of the Atlantic.” – Well, on average, the included studies did not achieve the 130 mm Hg target? Is it possible that the included studies did not see much efficacy due to the small decrease in SBP? Whether or not there is an issue in the new targeted SBP, it is not adequately addressed by the results of this review. The argument on potential performance bias (page 15) does not seem to be convincing either.

To target a SBP below 130 mm Hg does not mean actually reaching below 130. This is true for the SPRINT trial, referred to earlier by this reviewer, and especially true for clinical practice.

Whereas the drop in BP was small, it was achieved by adding one agent. Thus our review corresponds to the clinical situation where you have a patient with SBP 130-140 and want to know the effect of adding an extra pill. We have revised the first paragraph in the discussion to better reflect our analyses and findings.

The discussion on standardization was not very clear. The issues discussed should not happen with proper standardization.

Well, they do. We have already used twenty rows trying to explain this, despite it not being the main scope of this article. Further, we refer to the original paper where this was assessed. We fear that diving deeper into the standardization issue would impair readability for most of the readers of BMJ Open, since this is a clinical journal. If the editors are of a different opinion, please, let us know and we will revise accordingly.

Many places in the text need more clarification. Here are a few examples:
Page 7, first paragraph, "… because several antihypertensive agents are thought to have blood pressure independent effects on clinical outcomes in these settings". What are "blood pressure independent effects"? It helps to be more specific.

This has been clarified.

Page 7, second paragraph, what does it mean "we used one of our recent, more comprehensive systematic reviews for study selection"? More accurate description is helpful.

We have added a clause describing the scope of the previous review. For additional details, we cite the reference to the previous review.

Similarly, Page 8, the last sentence of the first paragraph, please improve the clarity.

We have added references for readers not familiar with selective reporting.

Page 17, "Although arguments can be made for including target-trials, lumping different populations and using standardization, all these approaches build on assumptions that the current analysis does not."

This comment is not clear on what needs to be revised, and we have therefore not revised it.

VERSION 2 – REVIEW

REVIEWER	Wuxiang Xie Peking University Clinical Research Institute, China
REVIEW RETURNED	26-Mar-2019

GENERAL COMMENTS	The authors response well to my comments. No additional comment.

REVIEWER	Rongwei (Rochelle) Fu Oregon health and Science university, Portland OR, USA
REVIEW RETURNED	14-Apr-2019

GENERAL COMMENTS	Thanks for the authors to address my comments. I have a few remaining comments: Basically this review synthesized blinded RCTs of patients with baseline SBP 130-140 mm Hg and the results in the primary prevention trials showed that the treatments reduced an average 3.4 mm Hg in SBP and there is no clinical benefit. Therefore the revised conclusion "Overall, the results presented here do not

	support such treatment, except for in patients with established CAD" is more appropriate. Could the authors comment on "Is it possible to have more SBP reduction with more effective treatment so there might be a clinical benefit"? The SPRINT trial did achieve treatment goals in terms of average SBP level. The current review demonstrated the ineffectiveness of the treatments in the included RCTs, but did not provide evidence supporting or not supporting the change of treatment goal. The revised manuscript stated that "this review serves as validation of the ACC/AHA systematic review findings": - It helps to add a sentence to very briefly describe the actual findings of the ACC/AHA systematic review". Strictly speaking, it is not "validation", but additional information given the differences in the two sets of trials. Page 17, "Although arguments can be made for including target-trials, lumping different populations and using standardization, all these approaches build on assumptions that the current analysis does not." Do you mean "all these approaches build on assumptions that the current analysis does not make"? It was not a complete sentence.

VERSION 2 – AUTHOR RESPONSE

Response (italics) to additional comments by reviewer 3:

Basically this review synthesized blinded RCTs of patients with baseline SBP 130-140 mm Hg and the results in the primary prevention trials showed that the treatments reduced an average 3.4 mm Hg in SBP and there is no clinical benefit. Therefore the revised conclusion "Overall, the results presented here do not support such treatment, except for in patients with established CAD" is more appropriate.
Could the authors comment on "Is it possible to have more SBP reduction with more effective treatment so there might be a clinical benefit"? The SPRINT trial did achieve treatment goals in terms of average SBP level.

We have added an additional sentence, in the limitations section on page 15, to clarify.

The current review demonstrated the ineffectiveness of the treatments in the included RCTs, but did not provide evidence supporting or not supporting the change of treatment goal. The revised manuscript stated that "this review serves as validation of the ACC/AHA systematic review findings": - It helps to add a sentence to very briefly describe the actual findings of the ACC/AHA systematic review". Strictly speaking, it is not "validation", but additional information given the differences in the two sets of trials.

We have added a sentence, in the introduction on page 5, about the ACC/AHA findings.

Page 17, "Although arguments can be made for including target-trials, lumping different populations and using standardization, all these approaches build on assumptions that the current analysis does not." Do you mean "all these approaches build on assumptions that the current analysis does not make"? It was not a complete sentence.

This has been revised.